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EXAMINER
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 6/14/93 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), 900 (9) days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-18, 19, 20 are pending in the application.
   Of the above, claims 3, 4, 8, 9, 11, 12, 16-18 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 2, 5-7, 10, 13-15, 19, 20. are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

This application should be reviewed for errors.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 5-7, 10, 13-15, 19 and 20 are examined in this Office Action. Claims 19 and 20 are newly added.

The provisional rejection of claims 1, 2, 5-7 13-15 and 19, 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 8, 27 and 30 of copending application serial no. 07/467,888 is maintained in view of the lack of amendments to the claims. Applicants have stated that response to these rejections will be made upon indication of allowable subject matter.

The provisional rejection of claims 1, 2, 5-7 13-15 and 19, 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 12-24 of copending application serial no. 07/803,285 is maintained in view of the lack of amendments to the claims. Applicants have stated that response to these rejections will be made upon indication of allowable subject matter.

The rejection of claims 1, 2, 5-7, 10 and newly added claims 19, 20 under 35 U.S.C. 112, first and second paragraphs, is maintained. Applicants' arguments, filed June 14, 1993, have been considered but not found to be persuasive. Applicants have argued that the claims should not be limited merely to anti-TGF-beta antibodies. Applicants have argued that the amendment to claims 1 and 6 have overcome the rejection since the inhibitory agent is defined by its ability to suppress the accumulation of a component of the extracellular matrix in the tissue. The agent is not defined by its ability to bind TGF-beta or to its receptor site. However, such agents read on general protein synthesis inhibitors. Therefore, the specification is

not commensurate with the scope of the claims. Note that the addition of claims 19 and 20 does not overcome the rejection of the other claims.

Applicants have argued that the claims now more specifically recite that the agent affects at least one component of the extracellular matrix in the tissue and that the net effect remains a reduction in the deleterious accumulation of extracellular matrix as well as an effective method for treating pathologies characterized by a deleterious accumulation of extracellular matrix. However, the specification is not commensurate with the scope of the claims since Applicants have only presented evidence showing the effect on biglycan and decorin.

The rejection of claim 5 under 35 U.S.C. 112, first and second paragraphs, is maintained. Applicants have argued that the newly submitted references have provided evidence beyond mere speculation regarding the relationship between deleterious extracellular matrix accumulations and TGF-beta in glomerulonephritis, liver disease and ARDS. However, contrary to Applicants' arguments, the specification is not enabling at the time the claimed invention was made for the scope of the claims. In addition, the newly submitted literature provides support for the Examiner's position, which is that the effects of TGF-beta are not well enough defined to provide a method of treating other diseases such as cirrhosis and ARDS. For example, the Gessner paper discloses that in cirrhosis the pathobiology of the disease changes over time (Figure 3) and therefore the use of antig-TGF-beta agents to treat the disease is not established.

The rejection of claims 1, 2, 5-7 10 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendments to the claims.

The rejection of claims 1, 6, 10 and newly added claims 19, 20, under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to an antibody is maintained. Applicants have argued that the examiner should withdraw the rejection since Example VIII of the

application shows that the peptide blocked the proteoglycan producing effect of exogenously added TGF-beta in cultures of rat mesangial cells and that the model is a scientifically accepted in vitro model. However, the cited example discloses an in vitro assay system using added TGF-beta and measuring the inhibition of the production of proteoglycan. It is well acccepted in the art that results obtained using an in vitro assay system do not necessarily extrapolate to an in vivo effect. Both claims 1 and 6 claim treatment of pathologies and pathologies are not treated in tissue culture dishes. As previously stated, Applicants have failed to disclose evidence showing that the peptides would work in an in vivo setting.

Applicants have argued that the article by Border, newly submitted, shows that decorin administered IV inhibited TGF-beta induced deposition of extracellular matrix in injured glomeruli from nephritic rats. However, the specification as filed fails to provide support for the above disclosed reference.

Claim 13 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "general protein inhibitor" is vague and unclear since the method or mode of inhibition is not evident and many are known in the art. Applicants presumably intended to claim a "protein synthesis inhibitor".

The rejection of claims 13-15 under 35 U.S.C. 102(b) is withdrawn in view of the amendments to the claims.

The rejection of claims 1, 2, 6, 7 and newly added claims 19, 20 under 35 U.S.C. 103 as being unpatentable over Connor et al is maintained. Applicants have argued that the authors make no conclusion regarding the ability of the antibodies to block TGF-beta's ability to induce accumulation of ECM and invite further experimentation. However, contrary to Applicants' arguments, Connor discloses that the intraocular fibrous tissue is

characterized by an extensive accumulation of extracellular matrix proteins (page 1661, column 2, paragraph 2) and states in the Abstract that TGF-beta was production was three times greater in vitreous aspirates from eyes with intraocular fibrosis. Connor further states that antibodies against TGF-beta could block the TGF-beta activity. Since anti-TGF-beta was shown to block activity of TGF-beta and TGF-beta was shown to increase in intraocular fibrosis, which is characterized by an increase in extracellular matrix production, one of the activities which was inhibited by anti-TGF-beta was the blocking of ECM production, lacking evidence to the contrary.

The rejection of claims 5 and 10 under 35 U.S.C. 103 as being unpatentable over Connor as applied to claims 1, 2, 6, 7, 19 and 20 above and further in view of MacKay is maintained. Applicants have argued that in MacKay all but one reported study was done on cultured glomerular endothelial, epithelial and mesangial cells which were substantially homogenous and no organ tissue culture or in vivo studies were disclosed. However, Mackay was cited to disclose the relationship between TGF-beta and the proliferation of glomerular cells and the accumulation of mesangial matrix in progressive glomercular nephritis. Connor was cited to disclose use of tissue and as previously stated, it would have been obvious to one of ordinary skill to substitute glomerular tissue for the ocular tissue of Connor. Therefore, Connor was cited to teach the use of tissue and adequately does so.

Applicants have argued that MacKay does not show or suggest that TGF-beta was responsible for the production of a component of the extracellular matrix in a tissue. However, Mackay was cited to disclose the relationship between TGF-beta and the proliferation of glomerular cells and the accumulation of mesangial matrix in progressive glomerular nephritis and when combined with the teachings of Connor, the combination of references discloses accumulation of extracellular matrix in response to TGF-beta.

Applicants have argued that MacKay fails to teach the methods of claims 5 and 10. However, the combination of references renders obvious the claims for reasons as stated above and previously in the prior Office Action.

Applicants have argued that there is no motivation to combine the references. However, contrary to Applicants' arguments, MacKay provides the motivation to combine the references on page 1160, Abstract, wherein it is stated "The presence of TGF-beta receptors on intact glomeruli and on each glomerular cell type and the demonstrated responsiveness of these cells to TGF-beta combine to suggest that potentially important interactions may occur between resident glomerular cells and TGF-beta in vivo". Thus, it would have been obvious to one of ordinary skill to use an antibody to TGF-betsa in order to interfere with the interaction between TGF-beta and glomerular cells in an in vivo setting since antibodies are known to be able to localize to particular tissues in vivo.

Note that Applicants' arguments concerning the presence of TGF-beta alone in an in vitro setting are not persuasive since there is no evidence of record to indicate that TGF-beta acts alone in an in vivo setting.

No claim is allowed.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE

EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)308-4227.

An inquiry concerning this communication should be directed to Examiner Suzanne Ziska, Ph.D., at telephone number 703-308-1217.

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800
10/4/93